FORM PTO-1390 (Modified) (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 085933/0117

		U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)
		unassigned
INTERNATIONAL APPLICATION NO. PCT/EP99/02715	INTERNATIONAL FILING DATE April 22, 1999	PRIORITY DATE CLAIMED April 23, 1998

TITLE OF INVENTION

A PROCESS FOR THE CONVERSION OF ECHINOCANDIN CLASS OF PEPTIDES TO THEIR C4-HOMOTYROSINE MONODEOXY ANALOGUES

APPLICANT(S) FOR DO/EO/US

Triptikumar MUKHOPADHYAY; Kenia JAYVANTI; Erra Koteswara Satya Vijaya KUMAR.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO (If known, see 37 C.F.R 1 50 unassigned 09/673836	INTERNATIONAL APPLICATION NO PCT/EP99/02715	ATTORNEY'S DOCKET NUMBER 085933/0117

17. ☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO.....$860.00	$860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $1000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))		

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	4	-	20	=		×	$18.00		
Independent Claims	1	-	3	=		×	$80.00		
Multiple dependent claim(s) (if applicable)							$270.0		
TOTAL OF ABOVE CALCULATIONS =								$860.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).								$0.00	
SUBTOTAL =								$860.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +									
TOTAL NATIONAL FEE =								$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +									
TOTAL FEES ENCLOSED =								$860.00	
							Amount to be: refunded	$	
							charged	$	

a. ☒ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $1460.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, DC 20007-5109

October 23, 2000

Patricia D. Granados
SIGNATURE

NAME PATRICIA D. GRANADOS

REGISTRATION NUMBER 33,683

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 085933/0117

In re patent application of

MUKHOPADHYAY et al.

Serial No.: Unassigned — Group Art Unit: Unassigned

Filed: October 23, 2000 — Examiner: Unassigned

For: A PROCESS FOR THE CONVERSION OF ECHINOCANDIN CLASS OF PEPTIDES TO THEIR C4-HOMOTYROSINE MONODEOXY ANALOGUES

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231
Box Patent Application

Sir:

Prior to examination on the merits of the above-identified application, please amend the applications as follows:

IN THE CLAIMS

Please amend the claims as follows:

3. (Amended) A process as claimed in [claims 1 to 3] claim 1, wherein the reduction reaction is carried out by hydrogenolysis with Raney nickel in ethanol at pH7 and room temperature.

4. (Amended) A process as claimed in [claims 1 to 3] claim 3, wherein the hydrogenolysis is carried out in the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin.

REMARKS

Applicants respectfully request entry of the foregoing amendment prior to the examination on the merits of the instant application. Should the Examiner have any questions or comments regarding the pending application or this preliminary amendment,

the Examiner is requested to call the undersigned.

If there are any fees due in connection with the filing of this Preliminary Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

October 23, 2000
Date

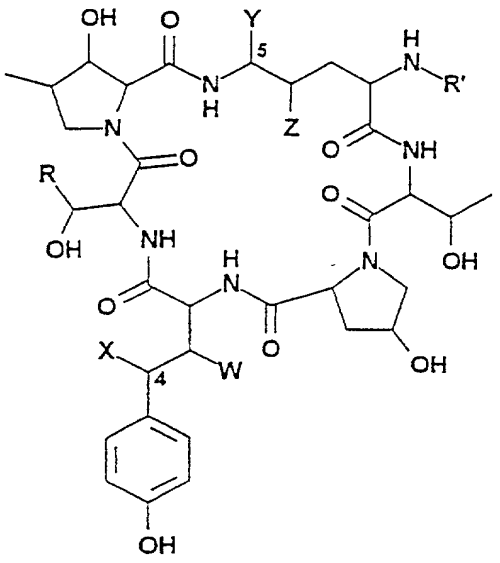
Patricia D. Granados
Reg. No. 33,683

FOLEY & LARDNER
Suite 500, 3000 K Street, N.W.
Washington, D.C. 20007-5109
(202) 672-5300

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

A process for the conversion of echinocandin class of peptides to their C4-homotyrosine monodeoxy analogues

This invention relates to a process for the conversion of echinocandin class of peptides of the formula I



(I)

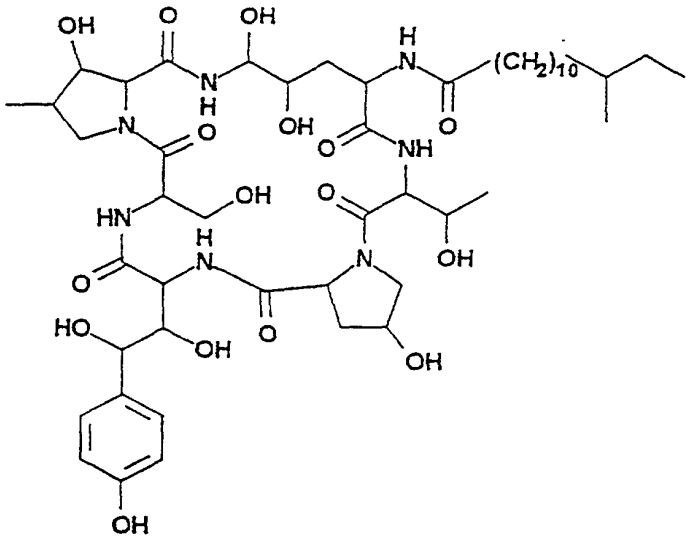
wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1.	Echinocandin B	OH	OH	OH	OH	CH_3	Linoleoyl
2.	Pneumocandin A_0	OH	OH	OH	OH	CH_2-$CONH_2$	10,12-Dimethyl-myristoyl
3.	Pneumocandin A_1	H	OH	OH	OH	CH_2-$CONH_2$	"
4.	Pneumocandin A_2	OH	OH	H	H	CH_2-$CONH_2$	"
5.	Pneumocandin B_0	OH	OH	OH	OH	CH_2-$CONH_2$	"
6.	Pneumocandin B_2	OH	OH	H	H	CH_2-$CONH_2$	"
7.	Pneumocandin C_0	OH	OH	OH	OH	CH_2-$CONH_2$	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

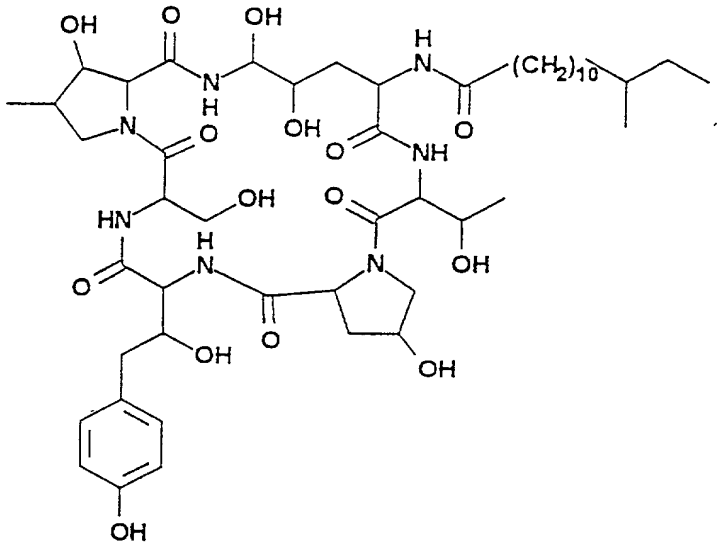
		W	X	Y	Z	R	R'
1.	Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH_3	Linoleoyl
2.	Deoxypneumocandin A_0	OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Deoxypneumocandin A_1	H	H	OH	OH	CH_2-$CONH_2$	"
4.	Deoxypneumocandin A_2	OH	H	H	H	CH_2-$CONH_2$	"
5.	Deoxypneumocandin B_0	OH	H	OH	OH	CH_2-$CONH_2$	"
6.	Deoxypneumocandin B_2	OH	H	H	H	CH_2-$CONH_2$	"
7.	Deoxypneumocandin C_0	OH	H	OH	OH	CH_2-$CONH_2$	"
8.	Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra-decanoyl,

particularly to a process for the conversion of mulundocandin (compound of the formula II)



(II)

to deoxymulundocandin (compound of the formula III)



(III)

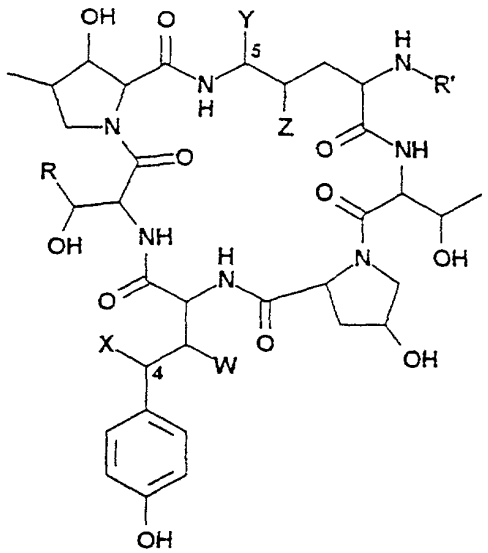
1,3-β-glucan synthesis inhibitors are effective antifungal agents against Candida albicans and also Pneumocystis carini, an opportunistic organism responsible for an often fatal pneumonitis among HIV patients and other immunocompromised hosts. Of all the structural classes of 1,3-β- glucan synthesis inhibitors, only the echinocandins received considerable attention [Ref : J. Med. Chem. 35, 198-200 (1992)]. Echinocandin class of peptides are cyclic hexapeptides having a lipophilic side chain.

Several methods for the conversion of echinocandins to the corresponding deoxy analogues under acidic conditions have been reported [Ref : Tetrahedron Letts., 33, 4529-4532 (1992); US Patent Appl. No. 222157 dated April 4, 1994]. The above methods involve selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues with prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group.

Mulundocandin [J.Antibiotics, 40, 275-280 and 281-289 (1987)] and deoxymulundocandin [Indian patent No. IN 169830 ; J.Antibiotics, 45, 618-623 (1992)] having antifungal properties were isolated from Aspergillus sydowii (Bainier and Sartory) Thom and Church var. Nov. Mulundensis Roy (culture no.HIL Y-30462). Deoxymulundocandin was found to possess better antifungal activity than mulundocandin. However, the production of deoxymulundocandin during the fermentation was 200 times less than that of mulundocandin.

We have found out by extensive research and experimentation that echinocandin class of peptides of the formula I may be converted to the corresponding C4-htyr monodeoxy analogues, particularly mulundocandin to deoxymulundocandin under neutral conditions. Accordingly, the object of the present invention is to provide a process for the conversion of echinocandin class of peptides of the formula I to the corresponding C4-homotyrosin monodeoxy analogues, particularly mulundocandin (compound of formula II) to deoxymulundocandin (compound of formula III).

According to the invention, there is provided a process for the conversion of echinocandin class of peptides of the formula I



(I)

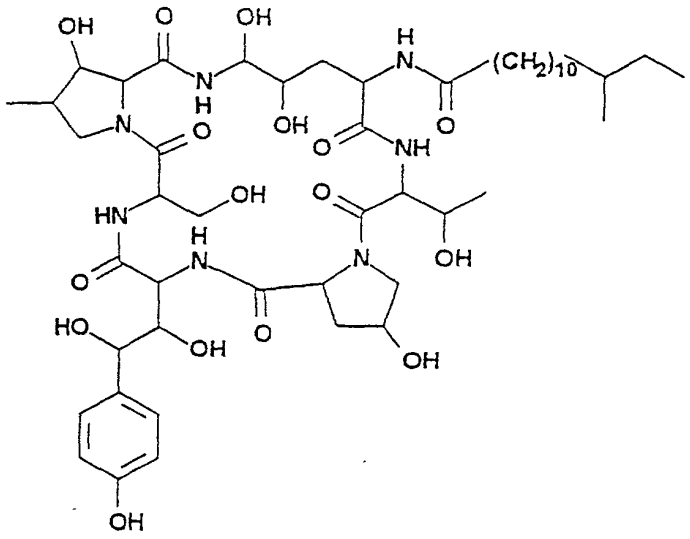
wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1.	Echinocandin B	OH	OH	OH	OH	CH_3	Linoleoyl
2.	Pneumocandin A_0	OH	OH	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Pneumocandin A_1	H	OH	OH	OH	CH_2-CO-NH_2	"
4.	Pneumocandin A_2	OH	OH	H	H	CH_2-CO-NH_2	"
5.	Pneumocandin B_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
6.	Pneumocandin B_2	OH	OH	H	H	CH_2-CO-NH_2	"
7.	Pneumocandin C_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

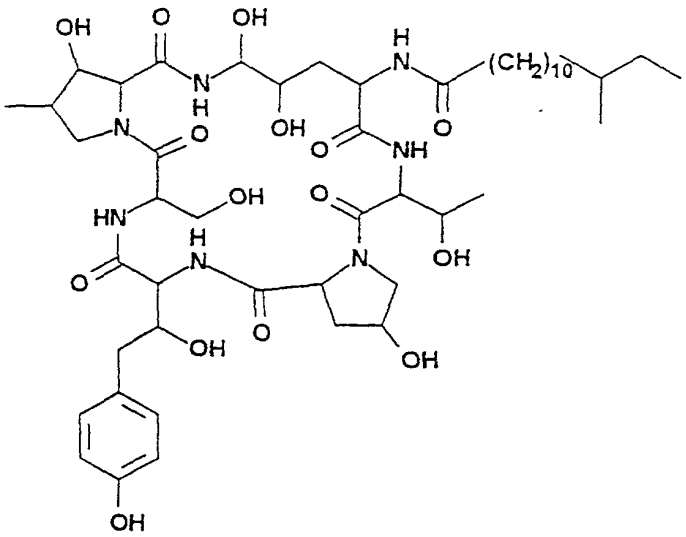
		W	X	Y	Z	R	R'
1.	Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH_3	Linoleoyl
2.	Deoxypneumocandin A_0	OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Deoxypneumocandin A_1	H	H	OH	OH	CH_2-CO-NH_2	"
4.	Deoxypneumocandin A_2	OH	H	H	H	CH_2-CO-NH_2	"
5.	Deoxypneumocandin B_0	OH	H	OH	OH	CH_2-CO-NH_2	"
6.	Deoxypneumocandin B_2	OH	H	H	H	CH_2-CO-NH_2	"
7.	Deoxypneumocandin C_0	OH	H	OH	OH	CH_2-CO-NH_2	"
8.	Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra-decanoyl

particularly to a process for the conversion of mulundocandin (compound of the formula II



(II)

to deoxymulundocandin (compound of the formula III)



which consists of a single step selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues particularly under neutral conditions without prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

The conversion of echinocandins to their monodeoxy analogues by selective reduction at C4-htyr may be effected by hydrogenolysis with Raney nickel in solvents such as methanol, ethanol, or dioxane at pH 3-9. Preferably, the selective reduction is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and room temperature in the ratio of 6.8 ml Raney nickel per millimole of mulundocandin.

The monodeoxy compounds of the invention may, for example, be purified from the crude reaction mixture as follows :

By fractionation using normal phase chromatography (using alumina or silica gel as stationary phase and eluents such as petroleum ether, ethyl acetate, dichloromethane, chloroform, methanol or combinations thereof), reverse phase chromatography (using reverse phase silica gel like dimethyloctadecylsilylsilica gel, also called RP-18 or dimethyloctylsilylsilica gel also called RP-8 as stationary phase and eluents such as water, buffers such as phosphate, acetate, citrate (pH 2-8) and organic solvents such as methanol, acetonitrile, acetone, tetrahydrofuran or combination of the solvents), gel permeation chromatography - using resins such as "Sephadex LH-20®" (Pharmacia Chemical Industries, Sweden), TSKgel Toyopearl HW (TosoHaas, Tosoh Corporation, Japan) in solvents such as methanol, chloroform or ethyl acetate or their combination or Sephadex G-10 and G-25 in water; or by counter-current chromatography using a biphasic eluent system made up of two or more solvents such as water, methanol, ethanol, *iso*-propanol, *n*-propanol, tetrahydrofuran, acetone, acetonitrile, methylene chloride, chloroform, ethylacetate, petroleum ether, benzene and toluene. These techniques may be used repeatedly or a combination of the different techniques may be used. Counter-

current chromatography (liquid-liquid chromatography) using a biphasic eluent system on ITO coil is preferred for purification of the compounds of the invention.

The following experimental example is illustrative of the present invention but not limitative of the scope thereof.

Example 1

Mulundocandin (220 mg, 2.2 mM) in ethanol (8 ml)) was stirred with 15 ml of W-2 Raney nickel (pH 7) in ethanol (30 ml) for 3 hours at room temperature. After standing for 15 minutes the supernatent solution was decanted and Raney nickel washed with 3 x 30 ml. ethanol with stirring and filtered. Combined ethanolic solutions were concentrated by distillation under a reduced pressure of 60-70 mm/Hg at 35° C to obtain 160 mg (75%) of crude deoxymulundocandin as a slightly green solid.

The crude product was purified by liquid-liquid chromatography on ITO coil using upper layer of CH_2Cl_2 : MeOH : *n*-PrOH :H_2O as the stationary phase and the lower layer as the mobile phase in an ascending mode. The coils (15 + 25 + 215 ml) were connected in series and a flow rate of 0.6 ml/min. at a piston stroke of 60 and pressure 0.5 bars was maintained. The purification of deoxymulundocandin was monitored both by bioactivity against *Candida albicans* and *Aspergillus niger* and by analytical High Pressure Liquid Chromatography (HPLC) [column : (10 x 0.4 cm + 3 x 0.4 cm) ODS-Hypersil, 10μ; mobile phase: 50:50 CH_3CN : H_2O ; flow rate : 1 ml/min; Wavelength : 220 nm.) The fractions (4.5 ml each) containing deoxymulundocandin were combined, concentrated by distillation under a reduced presssure of 60-70 mm/Hg at 35°C and lyophilized to yield pure deoxymulundocandin [65 mg (30% yield)]. Also recovered during the above purification of deoxymulundocandin was unreacted mulundocandin in 10% yield.

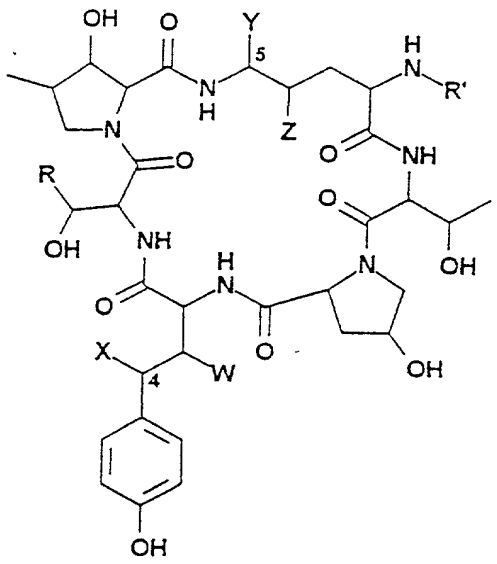
The semi-synthetic deoxymulundocandin was identical in all respects to the naturally isolated compound and the physico-chemical data is given in Table 1.

TABLE 1

Appearance :	White powder
Melting point:	170-172°C
$[\alpha]_D$:	- 36.6° (*c* 0.25, MeOH)
HPLC RT :	4.42 min
FAB-MS (Fast Atom: Bombardment mass)	1014.7 $(M + Na)^+$
^1H NMR (300 MHz,: CD_3OD)	Figure 1 of the accompanying drawings
^{13}C NMR (75 MHz, : CD_3OD)	Figure 2 of the accompanying drawings

Claims:

1. A process for the conversion of echinocandin class of peptides of the formula I



(I)

wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1.	Echinocandin B	OH	OH	OH	OH	CH_3	Linoleoyl
2.	Pneumocandin A_0	OH	OH	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Pneumocandin A_1	H	OH	OH	OH	CH_2-CO-NH_2	"
4.	Pneumocandin A_2	OH	OH	H	H	CH_2-CO-NH_2	"
5.	Pneumocandin B_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
6.	Pneumocandin B_2	OH	OH	H	H	CH_2-CO-NH_2	"
7.	Pneumocandin C_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below

		W	X	Y	Z	R	R'
1.	Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH_3	Linoleoyl
2.	Deoxypneumocandin A_0	OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Deoxypneumocandin A_1	H	H	OH	OH	CH_2-$CONH_2$	"
4.	Deoxypneumocandin A_2	OH	H	H	H	CH_2-$CONH_2$	"
5.	Deoxypneumocandin B_0	OH	H	OH	OH	CH_2-$CONH_2$	"
6.	Deoxypneumocandin B_2	OH	H	H	H	CH_2-$CONH_2$	"
7.	Deoxypneumocandin C_0	OH	H	OH	OH	CH_2-$CONH_2$	"
8.	Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra-decanoyl

which consists of a single step selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues under neutral conditions without prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

2. A process as claimed in claim 1, wherein Mulundocandin is converted to Deoxymulundocandin.

3. A process as claimed in claims 1 or 2, wherein the reduction reaction is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and room temperature.

4. A process as claimed in claims 1 to 3, wherein the hydrogenolysis is carried out in the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin.

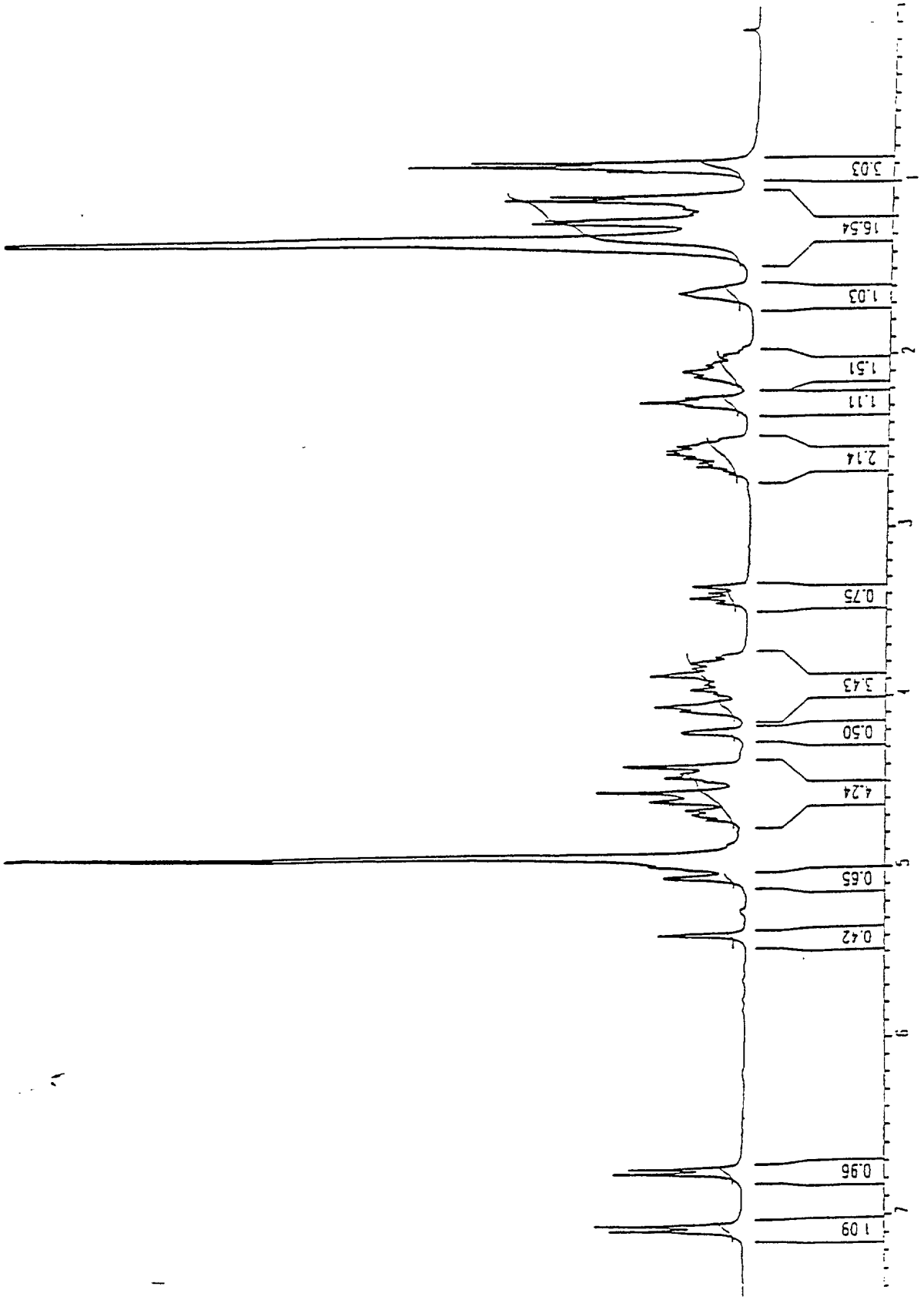

3.03
16.54
1.03
1.51
1.11
2.14
0.75
3.43
0.50
4.24
0.65
0.42
0.96
1.09
1
2
3
4
5
6
7
(ppm)

Fig. 1

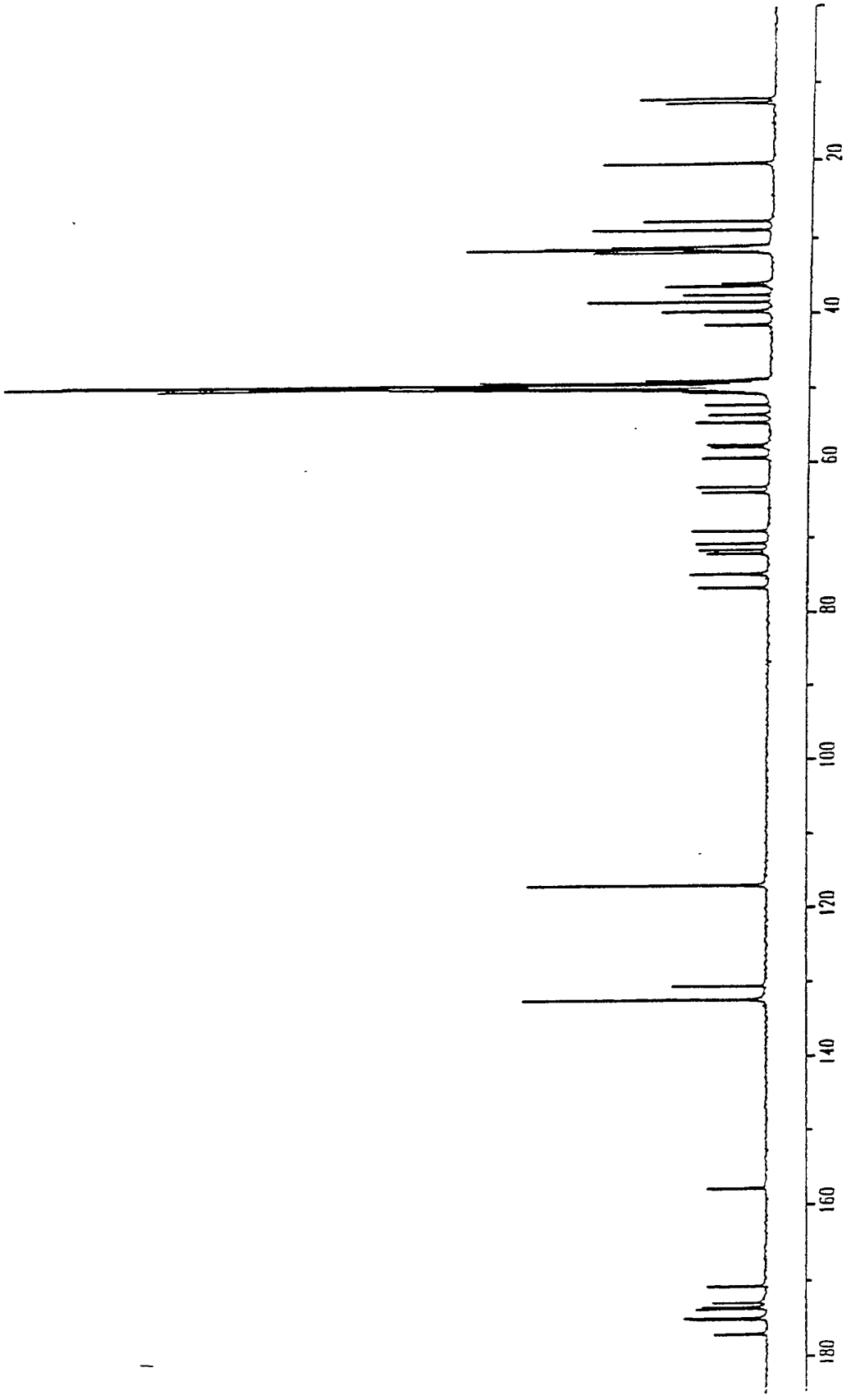


Fig. 2

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

A PROCESS FOR THE CONVERSION OF ECHINOCANDIN CLASS OF PEPTIDES TO THEIR C4-HOMOTYROSINE MONODEOXY ANALOGUES

(Attorney Docket No. 085933/0117)

the specification of which (check one)

___ is attached hereto.

__X__ was filed April 22, 1999 as PCT International Application Number PCT/EP99/02715

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?
98107397.6	EP	April 23, 1998	yes	no

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the following registered attorneys and agents of the law firm of FOLEY & LARDNER:

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to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

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I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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